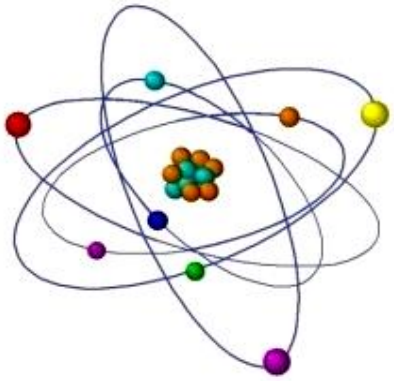
UV-C INDUCED GENOMIC INSTABILITY AND LONG-TERM EFFECTS OF ANTIOXIDANT PRODUCTION IN THE CHAMOMILE PLANT



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ABSTRACT. *The study of the mechanisms affecting single stress factor impact on long-term metabolic rearrangements is necessary for understanding the principles of plant protective reactions. The objective of the study was to assess the involvement of UV-C-induced genomic instability in induction plant long-term protective reactions. The study was carried out on two genotypes of chamomile, Perlyna Lisostepu (PL) variety and its mutant, using UV-C pre-sowing seed radiation exposure at dose levels 5–15 kJ/m2. Multiple DNA damages under different exposure doses were studied on plant tissues during the flowering stage using - ISSR-RAPD DNA marker PCR. In the cluster analysis of changes within the amplicon spectra as an integral group the Jacquard similarity index was used. The results of the study suggest that genomic instability is a link between the direct effects of UV-C exposure and stimulation of metabolic rearrangements at the final stages of ontogeny. A hypothetical scheme for the transformation of primary UV-C DNA damage into long-term maintenance of genomic instability signs has been proposed.*

Key words: Remote effects, genome instability, pre-sowing UV-C -irradiation

INTRODUCTION

The study of plant organisms' reactions to the action of various stresses is one of the main directions of plant biology. The diversity of various factors such as the physical nature of stressors, the action modes, the formation of protective and regenerative processes, the different organisms used in the experiment – all these make the area of the research almost boundless.

With all the variety of research area, the key questions are the emergence, development and the maintenance of stress factor response. As a first approximation stress factor reactions could be divided into "fast" taking from nanoseconds to minutes and hours, "medium" covering a part or whole plant ontogeny, and "long" characterised with the transgenerational effect [24, 42]. At the same time, they are differing with the formation duration and mainte- nance of both damage reactions and protective or reparative ones.

The easiest way to study the temporal characteristics of the stress response is the variant of

a single short-term exposure followed by the transformation of “fast” responses to the impact into long-term processes of damage development and the manifestation of protective UV radiation, especially UV-C exposure is a convenient stress factor when studying this range of the issues. There are fundamental differences between the effects of UV-A, UV-B and UV-C irradiation. UV-A and UV-B radiation are necessary for numerous physiological functions, their action is mediated by existing receptors for the perception of these wavelengths (cryptochromes, phototropins, UVR8) [15,38]. UV-C is almost completely absorbed by atmospheric oxygen and ozone; the exposure is not mediated by receptors, but is directly related to the damage of the oxidative nature of cell molecules, including DNA.

“Fast” responses to UV exposure are now reliably investigated. UV direct exposure is connected to the formation of DNA oxidation photo- products [22,25,26,35,40], stimulation of free radical processes and enzymatic formation of ROS [13,14,40].

A range of reactions has been studied that could be classified as “medium” in terms of the formation rate. Numerous studies have established a powerful effect of UV-C irradiation on the restructuring of plant metabolism. Ionizing and non-ionizing radiation stimulates secondary metabolism, including increasing formation of substances that have antioxidant, anticarcinogenic, immunomodulatory effects [1,5,11,12, 17]. Stimulation of the antioxidants’ formation associated with one-time pre-sowing UV-C exposure in low doses is detected at the final stages of plant ontogenesis [44]. Thus, there is an information concerning “medium” reactions and their type at the metabolic level, that is a direct indication of long-term disturbances in the redox background of the plant organism.

The genotoxicity of various parts of UV exposure spectrum at different doses is known. Currently, genome disorders under low doses of both direct and indirect exposure of various nature are considered as a special phenomenon so-called induced genomic instability. Induced genome instability (IGI) is an increase in the frequency of de novo occurrence of multiple genetic disorders in a significant part of the descendants of exposed cells, which is accompanied by an increase yield of reactive oxygen species (ROS), activation of transposable elements, and other epigenetic changes [18,34,37]. In recent decades the genome instability traits under UV exposure have been revealed using various methodological approaches, such as higher yield of both DNA fragmentation [6,10,13] and various chromosome aberrations on the first days after the exposure [3,6,18,23,41].

Comparison of the two data groups, especially the development of the genome instability phenomenon on the first days (5–10) after the exposure and maintenance of the high antioxidant yield during the final ontogenetic stage let us to conclude that genome instability is a link in the transformation of direct “fast” reactions into long-term stress response.

The study is devoted to testing the hypothesis about the existence of genomic instability signs during the flowering stage of plants under pre- sowing radiation exposure of seeds and the significant role of this phenomenon in the appearance of protective metabolic changes in the whole plant.

Pre-sowing irradiation of chamomile seeds was used followed by an assessment of the accumulation of low molecular weight antioxidants which are a well-identified marker of protective metabolism stimulation, and an assessment of indicators of damage to the primary DNA structure at the flowering stage of plants.

Thus, the objectives of the study was role assessment of UV-C- induced genomic instability in stimulation of plant remount, long-term protective reactions. Studying this issue can bring

closer understanding of the principles of the formation of a long-term response of plant organism to stress factor short-term exposure.

MATERIAL AND METHODS

The research in the conditions of the vegetation experiment was conducted on two genotypes of the pharmacy chamomile – Perlyna Lisostepu (PL), Ukrainian selection and its mutant (treated with herbicide Roundup MAKS 450 g/l glifosfate, in acidic equivalence 551 g/l). Seed material was received from the Research Station of Medicinal Plants of the Institute of Agroecology and Nature Management of the NAAS of Ukraine, Lubny. Previous studies of chamomile genotypes of pharmacy selection in different European countries have revealed a significant difference in physiological and biochemical characteristics of these two genotypes [32,44]. An assessment of intraspecific relationships [27] by ISSR-RAPD polymorphism using UPGMA software (available online at http://gen omes.urv.cat/UPGMA/) found that the Jacquard similarity index of these genotypes according to ISSR–sequences are 0.477, RAPD - sequences - 0.391 respectively. To date, the mutant of Perlyna Lisostepu is involved in variety testing: assessment of difference, homogeneity, stability of traits.

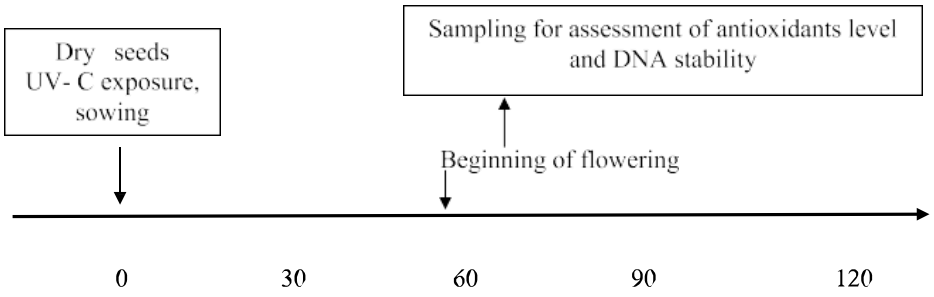

Fig.1. A generalized scheme of the experiment

A generalized scheme of the experiment is shown in Fig. 1. UV-C irradiation was conducted at doses of 5–15 kJ/m2 on OBM-150 M installation (Ukraine) with two Philips Special TUV 30 W lamps (Netherlands), dose rate - 3.4 W/m2, wavelength - 253.4 nm. The se- lection of the dose interval that stimulates the development of antioxi- dants without suppressing the yield of inflorescences was carried out in advance and secured by a patent [19]. There were grown 10 plants per pot with 1.5 kg of loamy soil. For one variant of the experiment were used 5 pots, ie 50 plants. For molecular analysis DNA was isolated from the vegetative mass of plants in the flowering phase, the material was selected by taking a small amount of tissue from all plants, followed by mixing and averaging immediately before DNA isolation. Conditions for collection, preparation and storage of pharmaceutical raw materials are described previously [32].

The study of rearrangements of the primary structure of DNA under conditions of different doses of UV-C exposure was carried by PCR using 8 ISSR and 10 RAPD primers (Tables 1 and 2). This method has become widespread in recent decades [20]. Focusing on the study of RAPD and ISSR microsatellite sequences was based on previous data that revealed the appearance of atypical amplicons in these se- quences, which indirectly indicated the

"rejection" of more serious DNA violations in "checkpoints" and mitosis [31]. ZymoResearch (Quick-DNA Plant/Seed Miniprep Kit) was used to isolate DNA according to the manufacturer's protocol. PCR was carried out using a GeneAmp PCR 2400 thermocycler (Applied Biosystems, USA). Checking the nativeness of the isolated DNA, as well as separating the products of PCR reactions, was carried out in a 1.7% agarose gel with TBE buffer, visualized in the presence of ethidium bromide on a UV transilluminator, and then photographed. When performing electro- phoresis in the "pocket" of the gel was made 5 µl of DNA solution. GeneRuler 50 bp was used as a molecular weight marker. Two types of primers were used for PCR: OPA and ISSR (Metabion, Germany) and a ready mixture of reagents for DNA amplification of PCR MIX 2x-R (Neogene, Ukraine).

The 25 µl PCR reaction mixture contained: 12.5 µl of MIX 2x-R PCR,

1.75 µl of primer, 5.75 µl of deionized water and 5 µl of total genomic DNA. Amplification with ISSR primers included the following steps: initial denaturation for 4 min at 94 ◦C, 40 cycles; denaturation at 94◦C - 45 s, annealing - 45 s (temperature differed for each primer, specified by

the manufacturer), elongation at 72 ◦C - 45 s; the final elongation lasted 7 min at 72 ◦C. Amplification with OPA primers included the following steps: initial denaturation for 5 min at 94 ◦C, 40 cycles; denaturation at 94◦C - 40 s, annealing - 40 s (temperature differed for each primer, specified by the manufacturer), elongation at 72◦C - 2 min; the final elongation lasted 10 min at 72◦C.

The nucleotide sequences of the primers are shown in Tables 1 and 2. Two indicators were used to characterize dose-depend changes in amplicon spectra using ISSR and RAPD DNA markers' analysis of both control and irradiated variants. The indicator "% of atypical amplicons" was calculated as the ratio of the number of amplicons which were different from the control to their total number. To assess the significance of the difference in average indicators for variants of the experiment, the non-parametric Van der Waerden X-test was used [21]. In the cluster analysis of changes within the amplicon spectra as an integral group the Jacquard similarity index was used [9]. Extraction of flavonoids and phenols was carried out by traditional methods [7] which was also used in the previous works of the authors [33,44]. SF-46 (Shimatzu UV-1280) spectrophotometer.

In the analysis of changes in the specific content of low molecular weight antioxidants, the average arithmetic values (X) and their root mean square deviations (Sx) were determined. The reliability of the differences between the variants of the experiment was assessed by the parametric Student's t-test, confidence interval, P = 0.95 [21].

RESULTS AND DISCUSSION

Obtained electrophoregrams (Figs. 2 and 3) showed significant differences in the number and length of the amplicons during PCR analysis with both ISSR and RAPD DNA markers in the control variants of the two investigated genotypes of chamomile and the appearance of amplicons of different lengths under irradiation.

The interpretation of these results should take into account the peculiarities of the effect of UV radiation on DNA.

In addition to direct DNA oxidative injury by UV-C, significant damage is caused by free radicals, reactive oxygen species, the formation of which is stimulated by UV exposure [26, 28, 29,40,43]. More specifically UV light can direct induce ROS by affecting the enzyme catalase and up-regulating nitric oxide synthase (NOS) synthesis. It may also cause a decrease in protein kinase C (PKC) expression leading to increased ROS production [14].

The appearance of atypical amplicons longer than the control ones after exposure indicates that UV-C irradiation leads not only to frag- mentation [6,13,29] but also to more complex chromatin reorganization, similar insertion, transposition and duplication.

The most massive occurrence of atypical amplicons in mutant under 15 kJ/m2 correlates (R = 0.84, confidence interval, P = 0.95) with an increased cytosine content in ISSR markers (Table 2) (Fig. 4B).

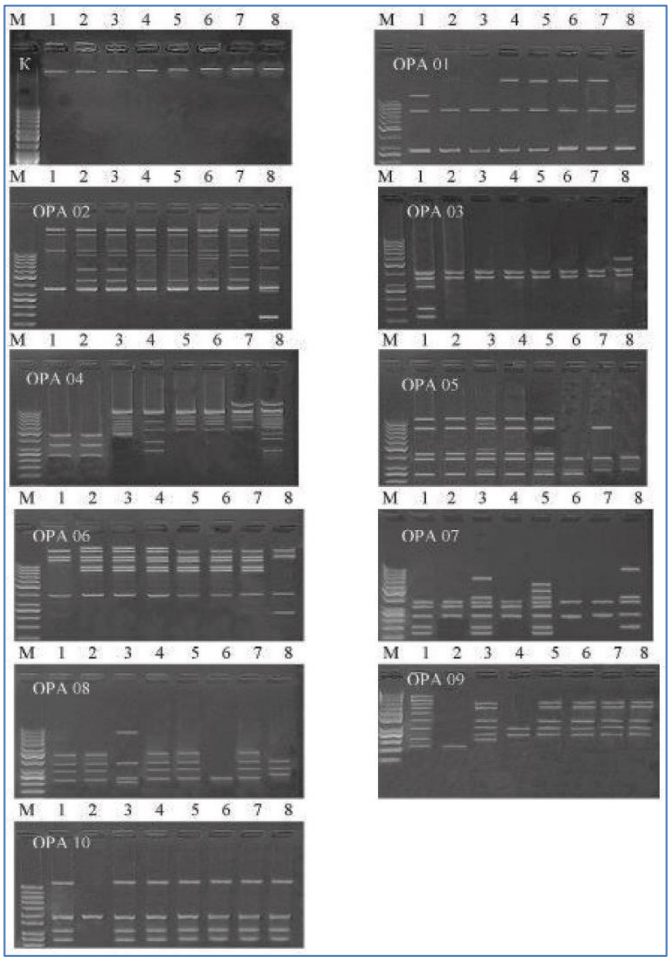

Fig. 2. Electrophoregram of RAPD-PCR products. C - control of DNA native- ness; M - molecular weight marker GeneRuler 50 bp;
1 - Perlyna Lisostepu, control;
2 - Perlyna Lisostepu 5 kJ/m2;
3 - Perlyna Lisostepu, 10 kJ/m2;
4 -Perlyna Lisostepu, 15 kJ/m2;
5 - mutant, control;
6 - mutant, 5 kJ/m2;
7 - mutant, 10 kJ/m2;
8 - mutant, 15 kJ/m2.

These data can be explained by the fact that during PCR with ISSR markers some secondary structures like hairpins are able to form that could cause the formation of DNA breaks during the replication [2,8]. Obviously, the probability of this effect increases with increasing dose and deviation of the primary DNA structure from the native one.

The appearance of double-stranded breaks and their erroneous repair is the main source of chromatin reorganization after irradiation [2,25] The phenomenon provides a certain contribution to the modification of the primary structure of DNA hypervariability, the formation of new microsatellites that are differ in length but not in nucleotide sequence, as replication and repair errors precisely in these DNA sequences [2,10,27].

The end results of these processes are significant rearrangements of the primary structure of DNA and chromatin, which shows a picture of changes in amplicon spectra during PCR analysis with different markers (Figs. 2 and 3).

Statistical assessment of the dependence on the dose of the average frequency of atypical amplicons according to PCR analysis with RAPD (Fig. 4A) and ISSR (Fig. 4B) markers using Van der Waerden's X-test indicates the existence of a significant difference between pairs of average values of the percentage of atypical amplicons at different doses for the analysis with both markers for the mutant. For Perlyna Lisostepu variety, there is no significant difference in the values of these indicators at doses of 10–15 kJ/m2 for the analysis with both markers.

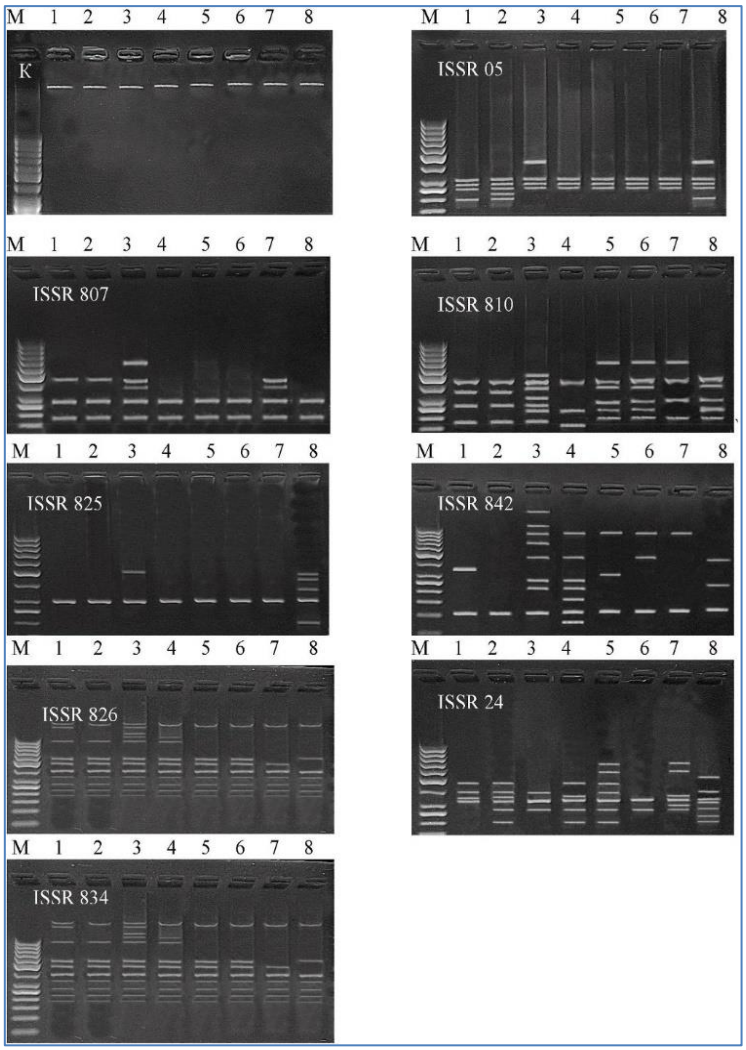

Fig. 3. Electrophoregram of ISSR PCR products. C - control of DNA nativeness; M - molecular weight marker GeneRuler 50 bp; 1 - Perlyna Lisostepu, control; 2- Perlyna Lisostepu 5 kJ/m2; 3 - Perlyna Lisostepu, 10 kJ/m2; 4 - Perlyna Lisostepu, 15 kJ/m2; 5 - mutant, control; 6 - mutant, 5 kJ/m2; 7 - mutant, 10 kJ/m2; 8 - mutant, 15 kJ/m2.

In case of PCR analysis with RAPD and ISSR markers for the mutant not only significantly lower appearance of atypical amplicons for doses of 5 and 10 kJ/m2 is observed in comparison with the maternal genotype (Fig. 4), but also significant difference in dose-curve type. A dose-dependent plateau in the range of 10–15 kJ/m2 that observing for Perlyna Lisostepu indirectly indicates reparative processes activation. The percentage of atypical amplicons consistently increases with increasing dose for the mutant. Thus, there is a difference in the activation of reparative processes for these two genotypes. Considering the second indicator of changes in the primary structure of DNA under UV-C exposure - the Jaccard similarity index between the spectra of amplicons of both control and irradiated variants. Tables 3 and 4 show the values of the Jaccard similarity index for the spectrum of amplicons obtained by PCR analysis with RAPD and ISSR markers separately for each of the genotypes.

There is a noticeable difference in the behavior of the similarity index of the genotypes depending on the dose. A monotonic decreasing amplicon spectra similarity with increasing the

dose of UV-C irradiation as a result of PCR with RAPD markers for Perlyna Lisostepu was indicated. A similar behavior of this indicator was revealed for the mutant in PCR analysis with ISSR markers. In the case of Perlyna Lisostepu variety irradiation at a dose of 15 kJ/m2 caused increasing similarity of amplicon spectra with the control after PCR analysis with ISSR markers. At the same time for the mutant a certain increasing similarity was indicated at both doses of 10 and 15 kJ/m2, moreover the yield of this indicator reached minimum values. Comparison of the behavior of the similarity index for the Perlyna Lisostepu variety with the dose dependence of the percentage of atypical amplicons of this genotype suggested that in this case the inclusion of reparative processes was observed.

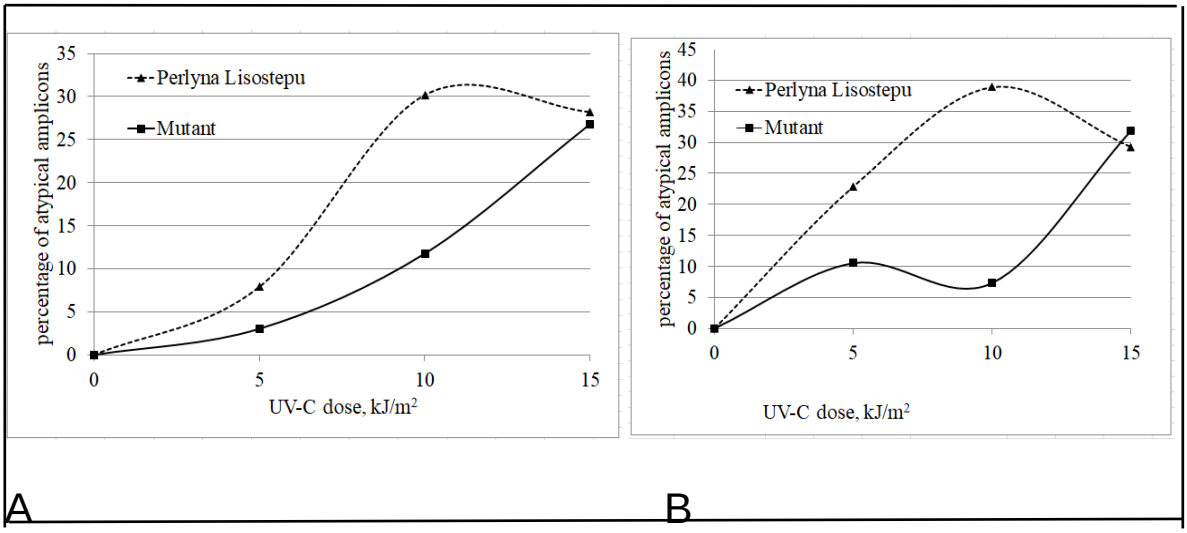

Fig.4 Dose dependences of frequency of atypical amplicons according to RAPD (A) and ISSR (B) PCR analysis data.

Thus, the main results of this stage of research are, firstly, the preservation of various rearrangements of the primary DNA structure during the flowering stage of plants growing from UV-C exposed seeds.

Secondly, a connection between the polymorphism of the primary structure of DNA in different genotypes and the nature of its rearrangement during UV-C irradiation was revealed; thirdly, significant difference in the general behavior of dose dependences of atypical amplicons' yield was indicated within two studied genotypes and certain difference in the dose dependences of the similarity spectra of amplicons from both exposed and control variants was showed.

The main conclusion from the obtained data is that differences in the primary structure of DNA affect its resistance to exogenous factors, and the degree of its disruption has different effect on the induction of both secondary and oxidative processes as well as reparative ones. Both of these phenomena can be explained from the point of view of the relationship between the primary structure of DNA and its nucleosomal organization [4, 36].

These effects are similar to the effects of presowing X-ray irradiation [32, 33]. However, there

were quantitative differences in the reorganization of the primary DNA structure under different types of irradiation. With UV-C exposure such a significant decrease in the similarity index was not observed as with the X-ray one. In other words, in general, there is a lower deviation through the DNA primary structure from the native one (Tables 3 and 4).

Analyzing the effect of pre-sowing exposure on the accumulation of phenols and flavonoids involved in the antioxidant protection of the cell and its individual structures including DNA.

Table 3

Dose dependence of the Jacquard similarity index of the amplicon spectra through each genotype indicated when performing RAPD DNA marker PCR.

Variants	P.L*. K	P.L. 5kJ/m2	P.L. 10kJ/m2	P.L. 15kJ/m2	Variants	M.K.	M**. 5kJ/m2	M. 10kJ/m2	M. 15kJ/m2
P.L. K.	1	0.818	0.833	0.783	M., K	1	0.792	0.875	0.769
P.L., 5kJ/m2		1	0.667	0.850	M., 5kJ/m2		1	0.905	0.708
P.L. ,10kJ/m2			1	0.708	M., 10kJ/m2			1	0.792
P.L., 15kJ/m2				1	M. 15kJ/m2				1

Variants P.L. P.L. 5kJ/m2 P.L. 10kJ/m2 P.L. 15kJ/m2 Variants M**.K M. 5 kJ/m2 M., 10kJ/m2 M.,

Table 4

Dose dependence of the Jacquard similarity index of the amplicon spectra through each genotype indicated when performing ISSR DNA marker PCR.

Variants	P.L.	P.L. 5kJ/m2	P.L. 10kJ/m2	P.L. 15kJ/m2	Variants	M**.K	M. 5 kJ/m2	M., 10kJ/m2	M., 15kJ/m2
P.L[a]. K.	1	0.944	0.739	0.895	M., K	1	0.947	0.850	0.800
P.L., 5 kJ/m2		1	0.696	0.944	M.,5 kJ/m2		1	0.800	0.842
P.L., 10kJ/m2	1		0.739		M., 10kJ/m2	1			0.667
P.L., 15kJ/m2				1	M., 15kJ/m2				1

[a] P.L- Perlyna Lisostepu, **M - mutant of the Perlyna Lisostepu.

It should be noted that the same specific content of the antioxidants was observed in controls of both genotypes. There are differences in the stimulation degree of the antioxidant yield in inflorescences for both genotypes under UV-C exposure. Antioxidant production was 3.5–4 times higher for mutant related to the same for Perlyna Lisostepu. Perhaps this effect was associated with lower atypical amplicons' yield in the mutant for the dose range of 5–10 kJ/m2 (Fig. 4). Flavonoid content dose dependence at 5 kJ/m2 for both genotypes entered the plateau. A significant increase in the specific content of phenols was observed only for the mutant with maximum at 10 kJ/m2 dose (Fig. 5B), followed by decreasing at 15 kJ/m2 to the control level. At the same dose there was an increase in the similarity of the primary DNA structure with the control according to PCR analysis with RAPD DNA markers (Table 3).

The increase in the level of antioxidants and the maintenance of this indicator at the same level coincided with the absence of a clear tendency to restore primary DNA structure. The plateau of the yield of atypical amplicons' dose dependence that could be considered as the activation of reparative processes, was confirmed by the second indi cator of the similarity index only for Perlyna Lisostepu genotype when performing PCR analysis with ISSR DNA markers.

When comparing the behavior of these two indicators, their infor- mational difference is revealed. This makes it possible to assume that it is not the number of atypical amplicons that is a signal for the stimu- lation of protective reactions, but rather the degree of false primary DNA structure and the appearance of its fragments of a certain size.

According to the results obtained, the decrease in DNA nativeness is accompanied by the stimulation of antioxidant defense (Fig. 5). It is most likely that this association is mediated by an increase in the yield of reactive oxygen species as an effect that accompanies the induced instability of the genome [39,40,41,43]

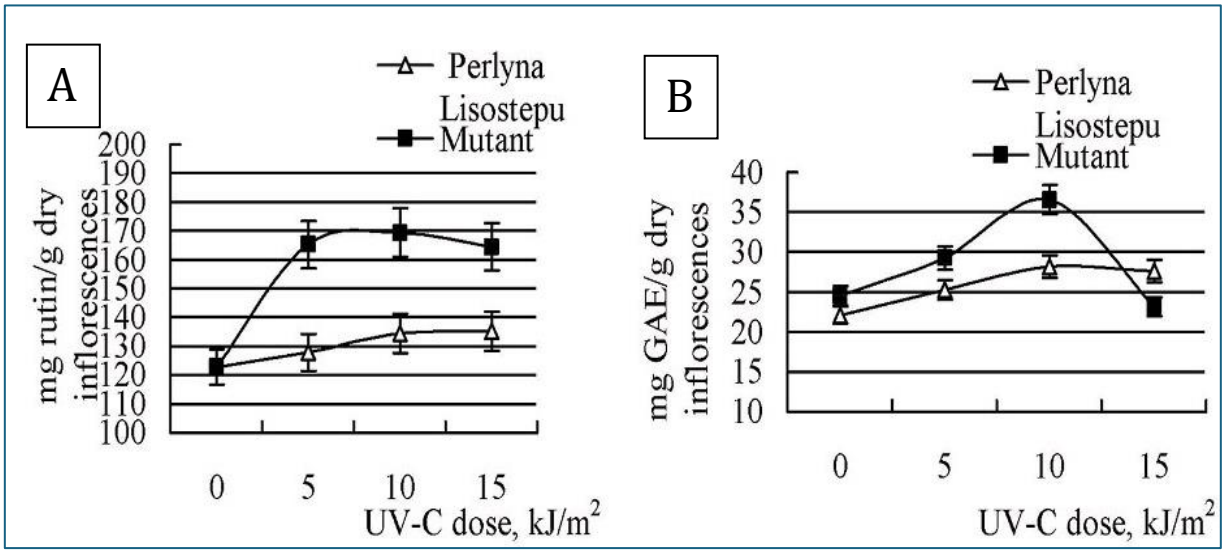

Fig. 5. Dose dependence of the total content of flavonoids (A) and phenols (B) in inflorescences of M. chamomilla of both Perlyna Lisostepu variety and its mutant. Confidence interval, P = 0.95.

The direct and feedback relationship between these two phenomena remains poorly understood [35,37]. However, the polyfunctional role of ROS is known. This group of compounds participate in the CIGI systems and various cell protective reactions including defense against foreign, “false” DNA [16,30]. The loss of DNA nativeness under UV-C exposure could be perceived by the cell’s defense systems as a “false” DNA and could stimulate the enzymatic formation of ROS. The effect of ROS to DNA leads to additional damage of the genetic material and triggers a chain reaction, i.e. genomic instability that could be stopped by reparative processes and restore the nativeness of the genetic material.

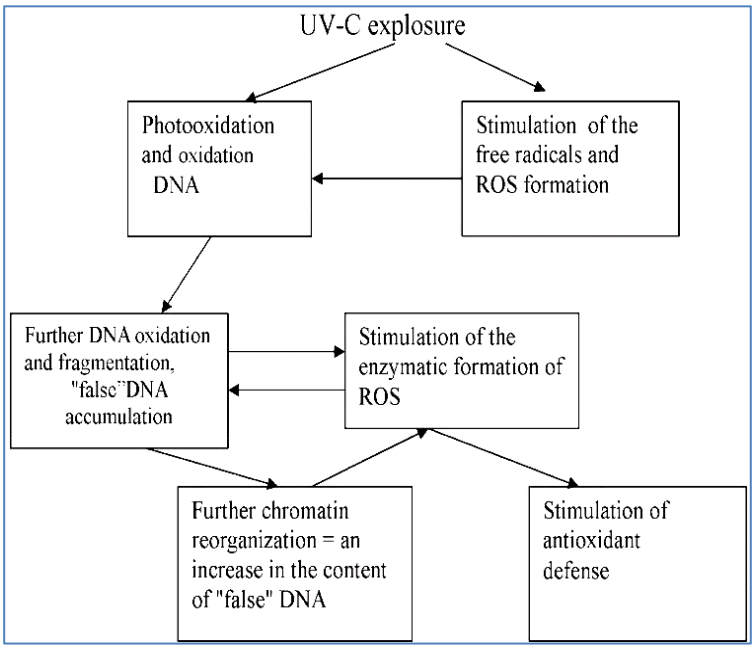

Fig. 6. Hypothetical scheme for the transformation of direct UV-C DNA damage into a chain reaction of maintaining IGI as a result of the interaction of “false” DNA with ROS.

Fig. 6. shows a hypothetical scheme for the transformation of direct UV-C induced DNA damage into long-term maintenance of the genomic instability effects due to both activation of ROS production and additional DNA nativity damage. The maintenance of IGI reflects the inter- action between DNA and ROS before switching on inducible repair processes.

This IGI management scheme is confirmed by the results of previous studies using X-ray irradiation. They showed the disappearance of stimulation of the accumulation of antioxidants during the restoration of the native DNA structure and, as a result, a decrease in the release of ROS [33]. At the same time, an important result of previous studies is the initially greater decrease in the similarity of the amplicon spectra for the control (native) ones. This confirms the data of other authors on the existence of a threshold for the initiation of inducible DNA forms [39]. Thus, the formation of stress response, the transformation of direct, “fast” reactions into long-term metabolic rearrangements are determined by the competitive (oxidative DNA

degradation and damage repair) and cooperative (antioxidant protection and repair) interactions.

Currently, the phenomenon of genomic instability has been comprehensively studied in biological models of varying complexity. The question of the mechanisms of transformation of one-time impacts into long-term effects has been repeatedly formulated in the scientific literature. However, the study of the affect of genomic instability on the formation of long-term metabolic changes has not been considered. The results of the study suggest that genomic instability is one of the main links between the direct, "fast" effects of exposure and initiate of defense responses at the final stages of ontogeny. Perhaps the data obtained bring closer the understanding of the principles of the formation of a long-term response of a plant organism to short-term exposure to a stress factor.

CONCLUSION

The results of the research have indicated that the formation of stress response and the transformation of direct, "fast" reactions into long- term metabolic rearrangements are determined by the competitive (oxidative DNA degradation and damage repair) and cooperative (antioxidant protection and repair) interactions.

The results of the study suggest that genomic instability is one of the main links between the direct, "fast" effects of exposure and stimulation of defense responses at the final stages of ontogeny.

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